

Remarks

These remarks are in response to the Office Action dated November 27, 2001. Claims 1, 3, 4, 6-10, 12, 13, 15-20, 23-25 and 27-35 have been amended. Claims 40-42 have been added. Support for the amended and new claims can be found throughout the specification. Attached is a marked-up version of the changes being made by the current amendment.

Applicants representatives wish to thank Examiner Whiteman for his helpful comments during the telephone interview of March 1, 2002. Claims 1-42 are pending and at issue. Applicant respectfully requests reconsideration of the present application.

I. Informal Matters

Applicants note that an IDS was filed on May 30, 2000, in connection with the present case. However, Applicants have not received a copy of the IDS signed by the Examiner. Applicants respectfully request that the Examiner provide a copy of the aforementioned IDS.

II. Claim Objections

Claim 9 is objected to for reciting a "hexon polypeptide gene." Claim 9 has been amended to recite a "hexon gene" as suggested by the Examiner..

Claim 33 is objected to for the recitation of "transforming or infecting into an adenovirus replication competent host cell two adenovirus replication defective sequences." Claim 9 has been amended to recite "transforming or infecting two adenovirus replication defective sequences into an adenovirus replication competent host cell, wherein the two sequences comprise..." as suggested by the Examiner.

In view of the amendments to the claims, Applicants request withdrawal of the present objections.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-20, 27-33, and 35-39 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Applicants respectfully traverse this rejection.

The pending claims have been amended to distinguish the nucleic acids of the present invention. For example, Applicants have amended the claims to recite an adenovirus "helper-dependent" nucleic acid sequence and an adenovirus "helper" nucleic acid sequence (see page 20, lines 3-12 of the specification for support). In view of the amendments to the claims, Applicants respectfully request that the present rejections be withdrawn.

IV. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-20, 27-33, and 35-39 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection. Applicants respectfully traverse this rejection.

The pending claims have been amended to distinguish the nucleic acids of the present invention. For example, Applicants have amended the claims to recite an adenovirus "helper-dependent" nucleic acid sequence and an adenovirus "helper" nucleic acid sequence (see page 20, lines 3-12 of the specification for support). In view of the amendments to the claims, Applicants respectfully request that the present rejections be withdrawn.

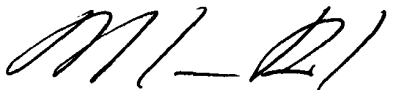
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In summary, for the reasons set forth herein, Applicant maintains that claims 1-42 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending. If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 678-5070. Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 3/27/02



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Version with markings to show changes made

In the claims:

Claims 1, 3, 4, 6-10, 12, 13, 15-20, 23-25 and 27-35 have been amended as follows:

1. (Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid [based on adenovirus serotype], the vector system comprising:

(a) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising: [a first]

(i) 5' and 3' adenovirus inverted terminal repeats (ITRs);

(ii) an adenovirus serotype-specific cis-acting packaging sequence; and

(iii) a heterologous nucleic acid;

(b) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

(i) [a second] 5' and 3' adenovirus ITRs;

(ii) an adenovirus serotype-specific cis-acting packaging sequence,

wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-acting protein; and

(c) [a nucleic acid sequence encoding] a polypeptide having activity of a [first adenovirus serotype] 52/55 kDa trans-acting protein [and lacking the activity of a second adenovirus serotype 52/55 kDa trans-acting protein] that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

2. The vector system of claim 1, wherein the adenovirus capsid, packaging and 52/55 kDa trans-acting protein encoding sequences are human adenovirus sequences.

3. (Amended) The vector system of claim 2, wherein the [first and second] helper-dependent and helper adenovirus serotypes are selected from the group consisting of adenovirus type 2 (Ad2), adenovirus type 5 (Ad5), adenovirus type 7 (Ad7), adenovirus type 12 (Ad12), adenovirus type 17 (Ad17), [or] and adenovirus type 40 (Ad40)[, and the first serotype differs from the second serotype].
4. (Amended) The vector system of claim 2, wherein the [first] helper-dependent adenovirus serotype is adenovirus type 5 and the [second] helper adenovirus serotype is adenovirus type 7.
5. (Amended) The vector system of claim 2, wherein the [first] helper-dependent adenovirus serotype is adenovirus type 7 and the [second] helper adenovirus serotype is adenovirus type 5.
6. (Amended) The vector system of claim 1, wherein the [first replication defective] helper-dependent adenovirus sequence [cannot] fails to produce a complete adenovirus capsid.
7. (Amended) The vector system of claim 6, wherein the [first replication defective] helper-dependent adenovirus sequence is encapsidated in a capsid comprising at least one polypeptide encoded by the [second replication defective] helper adenovirus sequence.
8. (Amended) The vector system of claim 6, wherein the [first replication defective] helper-dependent adenovirus sequence is [encapsidated] packaged in a capsid encoded by the [second replication defective] helper adenovirus sequence.
9. (Amended) The vector system of claim [1] 42, wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, penton gene, fiber gene or hexon [polypeptide] gene or combination thereof.

10. (Amended) The vector system of claim 1, wherein the [inability] failure to produce a functional 52/55 kDa trans-acting protein is due to a mutation in the sequence encoding the protein.
11. The vector system of claim 10, wherein the mutation is a missense mutation, a point mutation, a frameshift mutation or a deletion mutation.
12. (Amended) The vector system of claim 1, wherein the [second replication defective] helper adenovirus sequence further comprises [the] a nucleic acid sequence encoding the polypeptide having the activity of the [first serotype] 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid.
13. (Amended) The vector system of claim 1, wherein [the nucleic acid sequence encoding] the polypeptide having the activity of the [first serotype] 52/55 kDa trans-acting protein [further comprises an adenovirus replication competent host cell] that supports packaging of the helper-dependent adenovirus nucleic acid sequence is encoded by a nucleic acid sequence functionally-associated with the genome of an adenovirus replication competent host cell.
14. The vector system of claim 13, wherein adenovirus replication competent host cell is a 293 cell line.
15. (Amended) The vector system of claim 1, wherein the polypeptide having the activity of a [first serotype] 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence is a [first serotype] 52/55 kDa trans-acting protein.
16. (Amended) The vector system of claim 1, wherein the [first replication defective] helper-dependent adenovirus sequence lacks at least one nucleic acid sequence needed to produce a capsid and further comprises a nucleic acid sequence encoding a polypeptide having the activity of a [first adenovirus serotype] 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence.

17. (Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid [based on adenovirus serotype], the vector system comprising:

(a) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising: [a first]

(i) 5' and 3' adenovirus ITRs;

(ii) an adenovirus serotype-specific cis-acting packaging sequence; and

(iii) a heterologous nucleic acid; [and,]

(b) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

(i) 5' and 3' adenovirus ITRs;

(ii) an [second] adenovirus serotype-specific cis-acting packaging sequence[,]; and

(iii) a nucleic acid sequence encoding a polypeptide having the activity of a [first adenovirus serotype] 52/55 kDa trans-acting protein[, lacking the ability to produce a polypeptide having the activity of a second adenovirus serotype 52/55 kDa trans-acting protein] that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

18. (Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid [based on adenovirus serotype], the vector system comprising:

(a) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising: [a first]

(i) 5' and 3' adenovirus ITRs;

(ii) an adenovirus serotype-specific cis-acting packaging sequence; and

(iii) a heterologous nucleic acid;

b) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

- (i) 5' and 3' adenovirus ITRs;
- (ii) an [second] adenovirus serotype-specific cis-acting packaging sequence,
wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a
polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-
acting protein; and
- (c) a cell comprising a nucleic acid sequence encoding a polypeptide having the activity of a
[first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein,
wherein the replication defective adenovirus comprises a defective or modified
adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber
gene or a hexon gene, or a combination thereof.

19. (Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid [based on adenovirus serotype], the vector system comprising:

- (a) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) an [first] adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid;
- (b) a helper [second replication defective] adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) an [second] adenovirus serotype-specific cis-acting packaging sequence,
wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a
polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-
acting protein; and[,]
- (c) an expression cassette comprising a nucleic acid sequence encoding a polypeptide having the activity of a [first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein,
wherein the replication defective adenovirus comprises a defective or modified
adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber
gene or a hexon gene, or a combination thereof.

20. (Amended) A vector comprising a replication defective adenovirus sequence comprising:

(a) a [first] helper-dependent adenovirus serotype-specific cis-acting packaging sequence[,];

(b) a nucleic acid sequence encoding a functional [second] helper adenovirus serotype-specific 52/55 kDa trans-acting protein, wherein the [second] helper adenovirus serotype 52/55 kDa trans-acting protein does not have the activity of a [first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein, lacking the ability to produce a polypeptide having the activity of a [first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein,

wherein the replication defective adenovirus sequence comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

21. The vector of claim 20, further comprising at least one adenoviral nucleic acid sequence needed to produce an adenoviral capsid.

22. The vector of claim 21, further comprising sufficient adenoviral nucleic acid sequence to produce a complete adenoviral capsid when the vector is expressed in an adenovirus replication-competent host cell.

23. (Amended) The vector of claim 20, wherein the [first and second] helper-dependent and helper adenovirus serotypes are selected from the group consisting of adenovirus type 2 (Ad2), adenovirus type 5 (Ad5), adenovirus type 7 (Ad7), adenovirus type 12 (Ad12), adenovirus type 17 (Ad17), [or] and adenovirus type 40 (Ad40)[, and the first serotype differs from the second serotype].

24. (Amended) The vector of claim 23, wherein the [first] helper-dependent adenovirus serotype is adenovirus type 5 and the [second] helper adenovirus serotype is adenovirus type 7.

25. (Amended) The vector of claim 23, wherein the [first] helper-dependent adenovirus serotype is adenovirus type 7 and the [second] helper adenovirus serotype is adenovirus type 5.

26. A transformed or isolated infected cell comprising the vector system of claim 1 or the vector of claim 20.

27. (Amended) A kit for making adenovirus encapsidated replication defective nucleic acid sequences comprising:

(a) a helper-dependent [first] adenovirus nucleic acid [serotype cis-acting packaging] sequence comprising: [a first]

(i) 5' and 3' adenovirus inverted terminal repeats (ITRs);

(ii) an adenovirus serotype-specific cis-acting packaging sequence; and

(iii) a heterologous nucleic acid;

(b) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

(i) 5' and 3' adenovirus ITRs;

(ii) an [second] adenovirus serotype-specific cis-acting packaging sequence, wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-acting protein;[,] and

(c) a nucleic acid sequence encoding a polypeptide having the activity of a [first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

28. (Amended) The kit of claim 27, wherein [the nucleic acid sequence encoding] the polypeptide having the activity of the [first serotype] 52/55 kDa trans-acting protein [further comprises an adenovirus replication competent cell] that supports packaging of the helper-dependent adenovirus nucleic acid sequence is encoded by a nucleic acid sequence functionally-associated with the genome of an adenovirus replication competent host cell.

29. (Amended) The kit of claim 27, wherein the nucleic acid sequence encoding a polypeptide having the activity of a [first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein further comprises an expression cassette.

30. (Amended) The kit of claim 27, wherein the [second replication defective] helper adenovirus sequence further comprises the nucleic acid sequence encoding a polypeptide having the activity of a [first] helper-dependent adenovirus serotype 52/55 kDa trans-acting protein.

31. (Amended) A method of producing a replication defective encapsidated adenovirus gene transfer vector, comprising the following steps:

(a) transforming or infecting into adenovirus replication competent host cells

(i) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus inverted terminal repeats (ITRs);

an [first] adenovirus serotype-specific cis-acting packaging sequence; and
a heterologous gene;

(ii) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus ITRs;

an [second] adenovirus serotype-specific cis-acting packaging sequence,

wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a
polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-acting protein; and

(iii) a nucleic acid sequence encoding a polypeptide having the activity of a [first adenovirus serotype] 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence; and

(b) culturing the cells under conditions where the helper-dependent [first] replication defective adenovirus sequence is encapsidated to produce a replication defective adenovirus gene transfer vector,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

32. (Amended) A method of producing a replication defective encapsidated adenovirus gene transfer vector, comprising the following steps:

(a) transforming or infecting into an adenovirus replication competent host cell two adenovirus replication defective sequences, wherein the cell comprises a nucleic acid sequence encoding a polypeptide having the activity of an [first] adenovirus serotype 52/55 kDa trans-acting protein that supports packaging of a helper-dependent adenovirus nucleic acid sequence and fails to support packaging of a helper adenovirus nucleic acid sequence,

(i) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus inverted terminal repeats (ITRs);

an [first] adenovirus serotype-specific cis-acting packaging sequence; and
a heterologous gene;[, and]

(ii) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus ITRs;

an [second] adenovirus serotype-specific cis-acting packaging sequence,

wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a
polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-acting protein; and

(b) culturing the cells under conditions where the helper-dependent [first] replication defective adenovirus sequence is encapsidated to produce a replication defective adenovirus gene transfer vector,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

33. (Amended) A method of producing a replication defective encapsidated adenovirus gene transfer vector, comprising the following steps:

(a) transforming or infecting two adenovirus replication defective sequences into an adenovirus replication competent host cell [two adenovirus replication defective sequences], wherein the two sequences comprise:

(i) a helper-dependent [first replication defective] adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus inverted terminal repeats (ITRs);

an [first] adenovirus serotype-specific cis-acting packaging sequence[.];

a heterologous gene; and

a nucleic acid sequence encoding a polypeptide having the activity of a [first adenovirus serotype] 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence[.]; and

(ii) a helper [second replication defective] adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus ITRs;

an [second] adenovirus serotype-specific cis-acting packaging sequence,

wherein the helper adenovirus nucleic acid [lacking the ability] fails to produce a polypeptide having the activity of [a second] the helper adenovirus serotype 52/55 kDa trans-acting protein; and

(b) culturing the cells under conditions where the helper-dependent [first] replication defective adenovirus sequence is encapsidated to produce a replication defective adenovirus gene transfer vector,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

34. (Amended) The method of claim 31, 32, or 33 wherein the helper [second replication defective] adenovirus sequence further comprises [sufficient] an adenoviral nucleic acid sequence [to encode] encoding a complete adenoviral viral capsid.

35. (Amended) A vector for selectively packaging replication defective nucleic acid sequences in adenovirus capsids [based on adenovirus serotype], the vector comprising:
- (a) a replication defective adenovirus sequence comprising an adenovirus serotype 7 (Ad7) cis-acting packaging sequence[,];
 - (b) a nucleic acid sequence encoding a polypeptide having the activity of an adenovirus serotype 5 (Ad5) 52/55 kDa trans-acting protein[,]; and
 - (c) [sufficient] an adenoviral nucleic acid sequence [to] that encodes a viral capsid[, lacking the ability] and fails to encode or produce a polypeptide having the activity of an adenovirus 7 serotype 52/55 kDa trans-acting protein.
36. A pharmaceutical composition comprising an encapsidated replication defective adenovirus, made using the vector system of claim 1, substantially free of helper virus, and a pharmaceutically acceptable excipient.
37. The pharmaceutical composition of claim 36, wherein the pharmaceutical composition is 99% free of helper virus.
38. A method of delivering a heterologous nucleic acid to a cell comprising transforming or infecting a cell with the pharmaceutical composition of claim 36.
39. The method of claim 38, wherein the pharmaceutical composition is administered to a patient systemically, regionally or locally.

The following claims have been added:

- 40. A packaging cell line for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid, the cell line comprising:
- (a) a helper-dependent adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus inverted terminal repeats (ITRs);
 - (ii) an adenovirus serotype-specific cis-acting packaging sequence; and

- (iii) a heterologous nucleic acid;
- (b) a helper adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) an adenovirus serotype-specific cis-acting packaging sequence,wherein the helper adenovirus nucleic acid fails to produce a polypeptide having the activity of the helper adenovirus serotype 52/55 kDa trans-acting protein; and
- (c) a polypeptide having activity of a 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence,
 - wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

41. A packaging cell line for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid, the cell line comprising:

- (a) a nucleic acid sequence encoding a polypeptide having the activity of an adenovirus serotype-specific 52/55 kDa trans-acting protein;
- (b) a helper-dependent adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus inverted terminal repeats (ITRs);
 - (ii) an adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid;
- (c) a helper adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) an adenovirus serotype-specific cis-acting packaging sequence that fails to support the activity of the polypeptide having the activity of an adenovirus serotype-specific 52/55 kDa trans-acting protein,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof.

42. A vector system for selectively packaging a replication defective nucleic acid sequence in a virus capsid, the vector system comprising:

- (a) a helper-dependent adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' viral inverted terminal repeats (ITRs);
 - (ii) a first adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid,

wherein the helper-dependent adenovirus nucleic acid fails to produce a polypeptide having the activity of a serotype-specific 52/55 kDa trans-acting protein specific for the first adenovirus serotype-specific cis-acting packaging sequence;

- (b) a helper adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' virus ITRs;
 - (ii) a second adenovirus serotype-specific cis-acting packaging sequence,

wherein the helper adenovirus nucleic acid fails to produce a polypeptide having the activity of a serotype-specific 52/55 kDa trans-acting protein specific for the second adenovirus serotype-specific cis-acting packaging sequence; and

- (c) a nucleic acid encoding a polypeptide or a polypeptide having an activity of a serotype-specific 52/55 kDa trans-acting protein that supports packaging of the first adenovirus serotype-specific cis-acting packaging sequence and fails to support packaging of the second adenovirus serotype-specific cis-acting packaging sequence.